TOXICOLOGICAL REVIEW AND CRITERIA FOR EVALUATION OF EXPOSURE TO METHYL *TERT*-BUTYL ETHER IN DRINKING WATER

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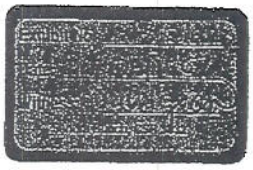

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PREFACE

The Bureau of Toxic Substance Assessment of the New York State Department of Health prepared this criteria document to assist in evaluating the health risks of exposure to methyl *tert*-butyl ether (MTBE) in drinking water. This document is not intended to be an exhaustive review of the MTBE literature, but is focused upon those data thought to be most relevant to human health risk assessment. The scientific literature was reviewed (last literature search update August 2000) and key studies evaluated to provide a qualitative and, to the extent possible, quantitative assessment of the toxicity of MTBE.

The criteria characterize the human health risks associated with exposure to MTBE in drinking water. The quantitative criteria developed in this document are not, in themselves, rules, or standards. They are based solely on data and scientific judgments on the relationship between MTBE drinking water and health risks, and do not reflect consideration of other factors, such as economic analysis and technological feasibility, which are evaluated when establishing regulatory requirements for drinking water contaminants.

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EXECUTIVE SUMMARY

Methyl *tert*-butyl ether (also called MTBE) is a colorless, synthetic liquid with an unpleasant taste and odor. MTBE is a gasoline additive used in the United States, including New York State, to reduce air pollution from gasoline engines. MTBE is a small, highly soluble molecule and does not bind strongly to soils. Gasoline spills and leaking gasoline storage tanks have contaminated groundwater with MTBE because MTBE travels rapidly to and through surface water and groundwater. The potential health effects of MTBE are of concern because many communities rely upon groundwater for their drinking water. This document reviews the current scientific literature on MTBE and derives criteria based on the potential for non-cancer and cancer health risks to humans exposed to MTBE in drinking water.

Studies on the human health effects of oral MTBE exposures were not found. Thus, the identification and evaluation of the potential human health effects from long-term exposure to MTBE in drinking water are based on the results of animal studies. The limited data on the pharmacokinetics of MTBE in humans and animals support this approach.

Animal data show that the targets for MTBE toxicity are the central nervous system, gastrointestinal tract, kidney, liver, and blood, and that MTBE can cause developmental effects at doses that also harm the pregnant adult animal. The animal data do not indicate that MTBE can cause reproductive effects. Based upon a review of the strengths and limitations of oral studies and selected inhalation studies for estimating potential human non-cancer risks from low-level oral doses of MTBE, the dose-response data from a subchronic study of systemic toxicity (diarrhea and blood chemistry changes) in rats are used to derive an adult drinking-water criterion of 200 micrograms per liter (ug/L) for non-cancer effects. The derived drinking-water criterion is protective of effects in children and of developmental effects observed in the offspring of female animals exposed to MTBE in air during pregnancy or before, during, and after pregnancy.

Given the available data, 200 ug/L is an estimate of the highest MTBE level in drinking water that is not likely to pose an appreciable non-cancer risk to chronically-exposed populations, including sensitive groups. The criterion is not an exact boundary between water levels that are safe and those that are not. For most people, exposure to water levels above, but near the criterion, will not cause non-cancer effects. However, the possibility exists, although unlikely,

that some people exposed to levels slightly below the criterion will show non-cancer effects. This uncertainty is unavoidable because inferring risks at dose levels substantially below the lowest daily dose associated with observable effects in animal studies is an uncertain process and our knowledge of the toxicological effects of oral doses is limited.

Various federal and state agencies have identified MTBE as an animal carcinogen. Oral and inhaled doses of MTBE caused cancer in laboratory animals. MTBE induced lymphomas/leukemias in female rats after gavage doses, testicular tumors (Leydig cell adenomas) in male rats after gavage doses or inhalation exposures, kidney tumors in male rats after inhalation exposures, and liver tumors in male and female mice after inhalation exposures. Based upon a review of the strengths and limitations of each data-set for estimating potential human cancer risks from low-level oral doses of MTBE, a quantitative estimate of the human cancer potency of MTBE in drinking water is based on dose-response data for testicular tumors (Leydig cell adenomas) in male rats given gavage doses of MTBE. The derived cancer potency factor is 3.2×10^{3} per milligram per kilogram body weight per day. This leads to a drinking-water criterion of 10 ug/L for cancer effects, which is the water concentration corresponding to the lower-bound estimate on the dose associated with an excess lifetime human cancer risk of one-in-one million. Drinking-water levels associated with excess lifetime human cancer risks of one-in-one-hundred-thousand and one-in-ten-thousand are 100 ug/L and 1,000 ug/L, respectively. Cancer potency factors based on the lymphoma/leukemia data or the inhalation studies are supportive of the selected potency factor, however, they may have greater uncertainty than the selected factor when used to assess the human cancer risk from low-level oral exposures to MTBE.

Because of the uncertainties associated with the animal-based cancer potency estimates, they cannot be used in an actuarial sense to predict the number of actual cancer cases in humans exposed to MTBE in drinking water. The exact degree of risk at low water levels may never be known because the risk is generally too small or too confounded by other factors to measure in the general population, particularly given the large background rate of cancer (lifetime risks of about 33%, or 333,000 per one million women, and 50% or 500,000 per one million men) in the general population.

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MTBE also induced mutations in L5178Y/TK mouse lymphoma cell cultures (*in vitro*) in two independent tests (ARCO, 1980; Mackerer et al., 1996). The ARCO results indicated mutagenicity only in the presence of S9. The Mackerer et al. (1996) results, which were from a modified version of the mouse lymphoma assay, indicated mutagenicity in the presence of S9 suspension but only when FDH was not present (i.e., the test was negative when FDH was present). These results suggest that formaldehyde may be partially responsible for the mutagenicity of MTBE.

In the fourth positive test, MTBE induced DNA strand breaks in the lymphocytes of male rats treated with gavage doses of MTBE (Lee et al., 1998). Male rats given gavage doses of 0, 400, or 800 mg/kg/day for 28 days showed reduced body weight gains and increased corticosterone levels. Lymphocytes collected from the body blood of the rats were isolated and run in an alkaline single-cell gel electrophoresis ("comet") assay. Four related parameters indicative of DNA strand breakage were increased in the 800 mg/kg/day group. This preliminary report has yet to be published as a full report.

Summary of the Genetic Effects of MTBE

MTBE was inactive in most tests of genetic activity. However, it was mutagenic the only time it was tested in a *Salmonella* strain (TA102) with a functioning DNA excision repair system (Williams-Hill et al., 1999). The results support the hypothesis of Williams-Hill and colleagues that the carcinogenic activity of MTBE may be dependent upon a functional excision repair system that attempts to remove alkyl adducts and/or oxidative base damage caused by direct interaction of MTBE or by its metabolites with DNA.

MTBE induced changes indicative of DNA damage in three of four mutation tests using lymphoid cells. MTBE was negative in an *in vivo* assay system with splenic lymphocytes collected from mice (i.e., the hprt mutation assay). The activity in lymphoid cells is particularly relevant given the increased incidence of lymphomas/leukemias in female rats exposed to oral doses of MTBE (Belpoggi et al., 1995, 1998).

Evaluations of the Human Carcinogenic Potential of MTBE by Other Organizations

Several groups or agencies have evaluated the animal data on the carcinogenicity of MTBE. The consensus opinion (Table 14) is that MTBE is an animal carcinogen because it caused lymphomas/leukemias in female rats, kidney tumors and Leydig cell adenomas in male rats, and hepatocellular tumors in mice.

Formal evaluations of the potential for MTBE to cause human cancer have been conducted by a Science Advisory Board committee under California's Safe Drinking Water and Toxic Enforcement Act of 1986 (better known as Proposition 65), a workshop of scientists convened by the International Agency for Research on Cancer (IARC), and various committees of the US National Toxicology Program (NTP) during the process to determine if MTBE should be listed in the 9th NTP Annual Report on Carcinogens. A summary statement of each finding is provided below.

- **Proposition 65** - On December 10, 1998, the Carcinogen Identification Committee of Science Advisory Board to the California EPA met to consider whether MTBE has been clearly shown, through scientifically valid testing according to generally accepted principles, to cause cancer. The Committee found that there was not a demonstrable majority within that Committee in favor of listing MTBE as a chemical that is known to the State of California to cause cancer. Nevertheless, the State of California's health-based drinking-water guideline and its drinking-water standard for MTBE are based on its cancer effects in animals (see Current Guidelines and Standards).

- **IARC (1999a) Summary** - Based on excepts from the monograph on MTBE found at the Internet site for IARC (http://www.iarc.fr), the workshop's conclusions are that: (1) there is inadequate evidence in humans for the carcinogenicity of MTBE; (2) there is limited evidence in experimental animals for the carcinogenicity of MTBE; and (3) MTBE is not classifiable as to its carcinogenicity to humans (Group 3).

- **NTP (2000) Summary** - The process of listing a chemical in the NTP's Annual Review of Carcinogens, which identifies chemicals known to be human carcinogens and chemicals reasonably anticipated to be human carcinogens, involves five separate reviews (Table 15). MTBE was evaluated for inclusion in the 9th Edition of the Annual Review as a chemical

Assuming a 70-kg adult drinks 2 liters of water per day for 70 years, an estimate of the MTBE water concentration corresponding to the lower bound estimate on the dose associated with an excess lifetime human cancer risk of one-in-one million is 10 ug/L (one significant figure). Other estimates of the water level associated with an excess lifetime risk of one-in-one million range from 8 to 40 ug/L. Several factors are important to the proper interpretation of these estimates.

- Whether or not MTBE causes cancer in humans is unknown. Thus, these estimates are not based on actual cancer cases in people exposed to MTBE and cannot be used to predict the actual number of people expected to get cancer from drinking water contaminated with MTBE.

- These estimates are hypothetical estimates based on extrapolating the observations of cancer in animals exposed to high doses for their lifetimes to humans exposed to much lower doses. For MTBE, scientific information documenting the accuracy of the extrapolation of animal data to humans is not available. Consequently, health-protective, scientifically reasonable choices are made to bridge the data gaps and do the extrapolation. Health-protective choices are those that more often than not lead to an overestimation of risk for typical people. In the assessment of cancer risks, these choices include:

    - The assumption that chemicals that cause cancer in animals at high doses also cause cancer in animals at low doses.
    - The choice to use the most sensitive animal study (sex, species, and tumor type).
    - The choice to use a high-to-low dose extrapolation model that gives a higher risk level for a given dose than most other models.
    - The choice to use the upper bound limit on the cancer risk estimate (95% upper confidence limit) rather than the average estimate.

- Given the number of health-protective choices, cancer risk estimates are typically considered "worst case" estimates; that is, the true risk is likely to be lower than the estimates and very unlikely to be higher than the estimate. Moreover, some scientists believe that the true risk